



**Medical Information Request: ZUSDURI™ (mitomycin) for intravesical solution and ENVISION patients excluded from efficacy analysis**

Thank you for your question regarding ZUSDURI and patients in the ENVISION clinical trial ([NCT05243550](#)).

ZUSDURI™ is indicated for the treatment of adult patients with recurrent low-grade intermediate-risk non-muscle invasive bladder cancer (LG-IR-NMIBC).<sup>1</sup>

**Background:**

The reverse thermal properties of ZUSDURI allow for local administration of mitomycin as a liquid under chilled conditions, with subsequent conversion to a semisolid gel depot following instillation into the bladder. Following instillation into the bladder, ZUSDURI forms a semisolid gel which dissolves in the urine. ZUSDURI contains mitomycin which is a violet to blue color and is excreted unchanged in the urine. During clinical studies, patients reported visible purple gel in urine for up to 24 hours (median 5 hours) after instillation.<sup>1-5</sup>

**Clinical Trial Design:**

ENVISION is a Phase 3, single-arm, multinational study evaluating the efficacy and safety of ZUSDURI (UGN-102) as a primary chemoablative therapy in 240 patients with LG-IR-NMIBC across 56 sites in the United States and Europe.<sup>4</sup>

The primary outcome measure of the trial was Complete Response Rate (CRR) at 3 months. Secondary endpoints are Duration of Response (DOR; up to 63 months), Durable Complete Response (DCR), Disease Free Survival (DFS) and Safety/tolerability of intravesical instillations in patients with LG-IR-NMIBC.

- Patients enrolled in ENVISION were eligible to receive six once-weekly intravesical instillations of ZUSDURI.
- The ZUSDURI admixture for intravesical instillations contains 75 mg mitomycin in 56 mL admixture
- All patients returned to the clinic approximately 3 months after the first instillation for determination of response to treatment. Assessment of response was based on visual observation (white light cystoscopy), histopathology of any remaining or new lesions by central pathology lab (if applicable), and interpretation of urine cytology by central pathology lab.
- Patients confirmed to have a complete response (CR) at the 3-month Visit, defined as having no detectable disease (NDD) in the bladder, entered the Follow-up Period of the study. Patients confirmed to have a non-complete response (NCR) underwent Investigator designated standard of care (SOC) treatment of remaining lesions and then entered the Follow-up Period of the study.
- During the Follow-up Period, patients returned to the clinic every 3 months for up to 24 months (i.e., 27 months after the first instillation) for evaluation of response. Patients who remain disease free at the 27-month Visit will continue to return to the clinic every 6 months for up to 36 months (i.e., 63 months after the first instillation) or until disease recurrence, disease progression, death, or the study is closed by the Sponsor, whichever occurs first.
- Patients confirmed to have a disease recurrence during the Follow-up Period or a disease progression at the 3-month Visit or during the Follow-up Period will undergo Investigator designated SOC treatment and have a separate End of Study (EOS) Visit performed. The timing of the EOS Visit will be approximately 3 months after SOC treatment of disease recurrence or progression.

**Patient Population:**

Inclusion Criteria	Exclusion Criteria
<ol style="list-style-type: none"><li>1. Capable of giving written informed consent, which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and the protocol.</li><li>2. Patient who has LG-NMIBC (Ta) histologically confirmed by cold cup biopsy at Screening or within 8 weeks before Screening.</li></ol>	<ol style="list-style-type: none"><li>1. Received Bacillus Calmette-Guérin (BCG) treatment for urothelial carcinoma (UC) within previous 1 year.</li><li>2. History of HG bladder cancer (papillary or carcinoma in situ [CIS]) in the past 2 years.</li><li>3. Known allergy or sensitivity to mitomycin that in the Investigator's opinion cannot be readily managed.</li></ol>

<p>3. History of LG-NMIBC requiring treatment with transurethral resection of bladder tumors (TURBT). Note: This refers to a previous episode(s) and not to the current episode for which the patient is being screened.</p> <p>4. Has intermediate risk disease, defined as having 1 or 2 of the following:</p> <ul style="list-style-type: none"> <li>○ Presence of multiple tumors;</li> <li>○ Solitary tumor &gt; 3 cm;</li> <li>○ Early or frequent recurrence (≥ 1 occurrence of LG-NMIBC within 1 year of the current diagnosis at the initial Screening Visit).</li> </ul> <p>5. Negative voiding cytology for high grade (HG) disease within 8 weeks before Screening.</p> <p>6. Has adequate organ and bone marrow function as determined by routine laboratory tests as below:</p> <ul style="list-style-type: none"> <li>○ Leukocytes ≥ 3,000 per <math>\mu</math>L;</li> <li>○ Absolute neutrophil count ≥ 1,500 per <math>\mu</math>L;</li> <li>○ Platelets ≥ 100,000 per <math>\mu</math>L;</li> <li>○ Hemoglobin ≥ 9.0 g/dL;</li> <li>○ Total bilirubin ≤ 1.5 x upper limit of normal (ULN);</li> <li>○ Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 × ULN;</li> <li>○ Alkaline phosphatase (ALP) ≤ 2.5 × ULN;</li> <li>○ Estimated glomerular filtration rate (eGFR) ≥ 30 mL/min.</li> </ul> <p>7. Has an anticipated life expectancy of at least the duration of the trial.</p> <p>8. Contraceptive use by men and women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. Women of childbearing potential (defined as premenopausal women who have not been sterilized), including female patients and female partners of male patients, must be willing to use 2 acceptable forms of effective contraception from enrollment through 6 months post-treatment.</p>	<p>4. Clinically significant urethral stricture that would preclude passage of a urethral catheter.</p> <p>5. History of:</p> <ul style="list-style-type: none"> <li>○ Neurogenic bladder;</li> <li>○ Active urinary retention;</li> <li>○ Any other condition that would prohibit normal voiding.</li> </ul> <p>6. Past or current muscle invasive bladder cancer (ie, T2, T3, T4) or metastatic UC.</p> <p>7. Current tumor grading of T1.</p> <p>8. Concurrent upper tract urothelial carcinoma (UTUC).</p> <p>9. Evidence of active urinary tract infection (UTI) that in the Investigator's opinion cannot be treated and resolved prior to biopsy and/or administration of study treatment.</p> <p>10. Is pregnant or breastfeeding.</p> <p>11. Has an underlying substance abuse or psychiatric disorder such that, in the opinion of the Investigator, the patient would be unable to comply with the protocol.</p> <p>12. History of prior treatment with an intravesical chemotherapeutic agent in the past 2 years except for a single dose of chemotherapy immediately after any previous TURBT.</p> <p>13. Has participated in a study with an investigational agent or device within 30 days of enrollment.</p> <p>14. Has previously participated in a study in which they received ZUSDURI.</p> <p>15. Has any other active malignancy requiring treatment with systemic anticancer therapy (eg, chemotherapy, immunotherapy, radiation therapy). Superficial cancers such as cutaneous basal cell or squamous cell carcinomas that can be treated locally are allowed.</p> <p>16. Has any other clinically significant medical or surgical condition that in the Investigator's opinion could compromise patient safety or the interpretation of study results.</p>
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**Efficacy Analysis vs Intention To Treat Population:**

In the ENVISION publication, all 240 patients screened and enrolled into the trial were assessed for efficacy and safety. The 240 patients were considered the Intent To Treat (ITT) or safety analysis population. ITT was defined as all patients enrolled and who received at least one dose of ZUSDURI.<sup>1,4</sup>

17 of 240 patients were excluded from FDA efficacy analysis due to protocol deviations. Per the ZUSDURI Prescribing Information (PI), those **17 patients were removed from the efficacy evaluation** resulting in an Efficacy Analysis population of 223 patients.<sup>1</sup>

**Patients Excluded from FDA Efficacy Analysis:**

The most frequent reason for exclusion from FDA Efficacy Analysis was enrollment without previous LG-NMIBC episode (n=10); of these, one reported previous high-grade disease, while others were newly diagnosed. Other reasons for exclusion are listed below:<sup>5</sup>

- 2 patients did not meet criteria for intermediate risk NMIBC.
- 2 patients had no residual bladder tumor at screening biopsy.
- 1 patient received chemotherapy within 2 years. (Exclusion criteria #12)
- 1 patient enrolled without prior TURBT to treat LG-NMIBC.
- 1 patient with high-risk disease enrolled while meeting all 3 criteria for intermediate risk NMIBC.



Study status of patients excluded from FDA Efficacy Analysis:

- 8 patients reported ongoing study status and continued follow-up assessments.
- 4 patients completed the study, of which one was due to death from cardiac failure (not related to procedure), and three due to progression or recurrence at various timepoints.
- 5 patients were discontinued from the study for various reasons. Two patients had no residual tumor prior to study start, one patient switched hospitals without disclosing outcome, one patient withdrew consent, and one patient discontinued due to cerebrovascular adverse event (not related to procedure).

Reason for Exclusion from FDA Analysis Set (Each row corresponds to an individual patient)	Longest Tumor Diameter (cm)	Tumor Count	Previous NMIBC Episodes Within 1 Year of Baseline Episode	Previous LG-NMIBC	Previous TURBT to Treat LG-NMIBC	Study Status	Primary Reason for Completion or Discontinuation	Number of Instillations	Disease Assessment Latest Month – Outcome
Patient enrolled without meeting any of the criteria for Intermediate Risk NMIBC	1	1	N	Yes	Yes	Completed	3-month NCR (residual disease) - recurrence or progression	6	15 -recurrence**
Patient enrolled without meeting any of the criteria for Intermediate Risk NMIBC	2	1	N	Yes	Yes	Ongoing	N/A	6	15 -CR
No residual bladder tumor at screening biopsy	6	1	Y	Yes	Yes	Discontinued	No residual tumor prior to instillation study start	6	6 -CR
Exclusion criteria #12 was violated - chemotherapy was administered < 2 years ago.	3.3	1	N	Yes	Yes	Ongoing	N/A	6	21 -CR
Patient enrolled without previous LG NMIBC Episode†	0.5	3	N	No	No	Completed	3-month CR - progression at 9-month	4	9 -recurrence
Patient enrolled without previous LG NMIBC Episode	1	2	N	No	No	Discontinued	Adverse Event*	6	12 -CR
Patient enrolled without previous LG NMIBC Episode	3.8	2	N	No	No	Ongoing	N/A	6	15 -CR**
Patient enrolled without previous LG NMIBC Episode	4.6	1	N	No	No	Completed	Death any time after first instillation***	6	N/A
Patient enrolled without previous LG NMIBC Episode	1	2	N	No	No	Ongoing	N/A	6	15 -CR
Patient enrolled without previous LG NMIBC Episode	4.9	7	N	No	No	Ongoing	N/A	6	15 -CR
Patient enrolled without previous LG NMIBC Episode	0.6	2	N	No	No	Ongoing	N/A	6	15 -CR
Patient enrolled without previous LG NMIBC Episode	1.5	3	N	No	No	Discontinued	Pt switched hospitals and did not disclose outcome info.	6	3 -progression
Patient enrolled without previous LG NMIBC Episode	1.8	4	N	No	No	Ongoing	N/A	6	15 -CR
Patient enrolled without prior TURBT to treat LG NMIBC	1.5	2	N	Yes	No	Ongoing	N/A	6	21 -CR
No residual bladder tumor at screening biopsy	N/A	2	N	Yes	Yes	Discontinued	No residual tumor prior to study start	6	3 -CR
High Risk Patient enrolled while meeting all 3 criteria for Intermediate Risk NMIBC	7	10	Y	Yes	Yes	Completed	3-month NCR (progression)	6	3 -progression
Patient enrolled without previous LG NMIBC Episode	1	1	N	No	No	Discontinued	Withdrawal of consent	6	12 -CR

\*Cerebrovascular accident – not related to procedure

\*\* Received standard of care determined by treating physician

\*\*\*Cardiac failure – not related to procedure

† Previous HG NMIBC

FDA, Food and Drug Administration; NMIBC, non-muscle invasive bladder cancer; TURBT, transurethral resection of bladder tumor; LG, low-grade; NCR, non-complete response; CR, complete response

**Safety:**

In the Phase 3 ENVISION study, 240 patients were analyzed for safety<sup>1</sup>:

- The most common ( $\geq 10\%$ ) adverse reactions, including laboratory abnormalities, that occurred in patients treated with ZUSDURI were increased creatinine, increased potassium, dysuria, decreased hemoglobin, increased aspartate aminotransferase, increased alanine aminotransferase, increased eosinophils, decreased lymphocytes, urinary tract infection, decreased neutrophils, and hematuria.
- Serious adverse reactions occurred in 12% of patients who received ZUSDURI, including urinary retention (0.8%) and urethral stenosis (0.4%). A fatal adverse reaction of cardiac failure occurred in 1 (0.4%) patient receiving ZUSDURI.
  - Three patient deaths were reported in the safety analysis set; investigators assessed these were not related to study treatment. There was one listing of death due to unknown reason in a patient with medical history of hypertension, myocardial ischemia, and chronic bronchitis. There was one listing of death due to pneumonia in a patient with medical history of hypertension, coronary artery disease, chronic kidney disease, and chronic obstructive pulmonary disease. There was one listing of death due to cardiac failure in a patient with medical history of aortic valve disease and cardiac failure.<sup>5</sup>
- Dosage interruption of ZUSDURI due to adverse reactions occurred in 10% of patients. Adverse reactions ( $\geq 2\%$ ) which required dosage interruption were urinary tract infection (2.5%) and dysuria (2.5%).
- Permanent discontinuation of ZUSDURI due to an adverse reaction occurred in 2.9% of patients, including 1.7% who discontinued due to a renal or urinary disorder.

Please refer to the Full Prescribing Information for ZUSDURI [here](#).

**ZUSDURI IMPORTANT SAFETY INFORMATION:****Contraindications**

ZUSDURI is contraindicated in patients with perforation of the bladder or in patients with prior hypersensitivity reactions to mitomycin or any component of the product.

**Warnings and Precautions****Risks in Patients with Perforated Bladder**

ZUSDURI may lead to systemic exposure to mitomycin and severe adverse reactions if administered to patients with a perforated bladder or to those in whom the integrity of the bladder mucosa has been compromised. Evaluate the bladder before the intravesical instillation of ZUSDURI and do not administer to patients with a perforated bladder or mucosal compromise until bladder integrity has been restored.

**Embryo-Fetal Toxicity**

Based on findings in animals and mechanism of action, ZUSDURI can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of mitomycin resulted in teratogenicity. Advise females of reproductive potential to use effective contraception during treatment with ZUSDURI and for 6 months following the last dose. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with ZUSDURI and for 3 months following the last dose.

**Adverse Reactions****Common Adverse Reactions**

The most common ( $\geq 10\%$ ) adverse reactions, including laboratory abnormalities, that occurred in patients treated with ZUSDURI were increased creatinine, increased potassium, dysuria, decreased hemoglobin, increased aspartate aminotransferase, increased alanine aminotransferase, increased eosinophils, decreased lymphocytes, urinary tract infection, decreased neutrophils, and hematuria.

**Additional Adverse Reactions Information**

Clinically relevant adverse reactions occurring in  $<10\%$  of patients who received ZUSDURI included increased urinary frequency, fatigue, urinary incontinence, urinary retention, urethral stenosis, genital pain, urinary urgency, genital edema, genital pruritus, genital rash, urethritis, acute kidney injury, balanoposthitis, and



nocturia.

### **Use in Specific Populations**

#### **Lactation**

Because of the potential for serious adverse reactions in a breastfed child, advise women not to breastfeed during treatment with ZUSDURI and for 1 week following the last dose.

#### **Preparation and Administration Information**

ZUSDURI is to be administered by intravesical instillation only. Do not administer ZUSDURI by pyelocalyceal instillation or by any other route.

ZUSDURI must be prepared and administered by a healthcare provider. To ensure proper dosing, it is important to follow the preparation instructions found in the ZUSDURI Instructions for Pharmacy and administration instructions found in the ZUSDURI Instructions for Administration.

ZUSDURI may discolor urine to a violet to blue color following the instillation procedure. Advise patients for at least 24 hours post-instillation to avoid urine contact with skin, to void urine sitting on a toilet, and to flush the toilet several times after use. Advise patients to wash hands, perineum or glans with soap and water after each instillation procedure.

ZUSDURI is a hazardous drug. Follow applicable special handling and disposal procedures.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit <http://www.fda.gov/medwatch> or call 1-800-FDA-1088. You may also report side effects to UroGen Pharma at 1-855-987-6436.

**Please see accompanying Full Prescribing Information, Instructions for Pharmacy and Instructions for Administration.**

#### **References:**

1. ZUSDURI™ (mitomycin) for intravesical solution. Prescribing Information. UroGen Pharma; 2025.
2. ZUSDURI™ (mitomycin) for intravesical solution. Instructions for Pharmacy (IFP)
3. ZUSDURI™ (mitomycin) for intravesical solution. Instructions for Administration (IFA)
4. Prasad SM, Shishkov D, Mihaylov NV, et al. Primary chemoablation of recurrent low-grade intermediate-risk nonmuscle-invasive bladder cancer with UGN-102: A single-arm, open-label phase 3 trial (ENVISION). *J Urol.* 2025;213(2):205-16.
5. Data on file. UroGen Pharma.

ZUSDURI™ is a trademark and UroGen® is a registered trademark of UroGen Pharma, Ltd.